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A systematic review and meta-analysis on the prevalence of Dupuytren Disease in the general population

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- Data analysis.
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Abstract

Background

Dupuytren Disease (DD) is a fibroproliferative disease of palmar fascias of the hand. The prevalence of DD has been the subject of several reviews, though an accurate description of the prevalence range in the general population, and of the relation between age and DD is lacking.

Methods

A systematic review was performed by searching Embase and Pubmed on database specific mesh terms, and in title and abstract for “Dupuytren”, “incidence”, and “prevalence”. Two reviewers independently assessed the papers using inclusion and exclusion criteria, and rated the included studies with a quality assessment instrument. In a meta-analysis the median prevalence, as function of age by gender, was estimated, accompanied with 95% prediction intervals. The observed heterogeneity in prevalence was investigated with respect to the quality of the study.

Results

Twenty-three of 199 unique identified papers were included. Number of participants ranged from 37 to 97,537, aging 18-100 years. Prevalence varied from 0.6-31.6%. The quality of studies differed, but could not explain the heterogeneity between studies. The median prevalence was estimated at 12%, 21%, and 29% at ages 55, 65, and 75 respectively, based on the relationship between age and prevalence determined from ten studies.

Conclusions

We have been able to describe a prevalence range of DD in the general population. Furthermore, the relationship between age and prevalence of DD is given per gender, including 95% prediction intervals. Hereby, it is possible to determine the prevalence at a certain age for the total general population, and for men and women separately.

Level of Evidence: Prognostic/Risk Studies, III

Introduction

Dupuytren Disease (DD) is a fibroproliferative disease which affects some of the palmar fascias of the hand. This results in the development of nodules and cords, which eventually may contract and give rise to flexion contractures of the affected fingers.

The origin of DD has been attributed to both genetic and environmental factors. The results of several family studies, and more specific twin studies, suggested that DD has a strong genetic component.¹⁻³ In 2011, Dolmans et al. performed a genome wide association study in which nine genes that are associated with DD were identified.⁴

Some environmental risk factors that have been associated with the presence of DD include excessive alcohol consumption, smoking, manual work and hand trauma.^{5,6} In addition, several diseases, such as diabetes mellitus and epilepsy, are thought to play a role in the etiology of DD.⁷⁻⁹ However, the role of these risk factors and diseases is not fully cleared, and the results of different studies are occasionally conflicting.

Many articles about the prevalence of DD have been published.¹⁰⁻¹⁵ In these articles there is a wide range of prevalence rates, varying from 0.2% to 56%^{16,17}, as reported by Hindocha et al. in their literature review.¹⁸ This wide range, in our opinion, may at least partly be caused by the great heterogeneity between study populations, i.e. general population, participants with certain risk factors as well as patients with specific diseases. Suboptimal design of the included studies may also be a reason for the wide range.

Until now, no systematic review was conducted to scrutinize the prevalence rates specifically in the general population. It is assumed that life expectancy will increase considerably in the coming decades¹⁹, and from our clinical experience we know that DD is a chronic disease of the elderly. Therefore, it will be important to enhance our knowledge about prevalence rates in the general population, and to be aware of changes in the prevalence across age. Furthermore, new treatment options have emerged, such as radiotherapy, percutaneous needle fasciotomy, and collagenase injection, and prevalence rates may be used to evaluate their cost effectiveness.

The aim of this study is to come to a more accurate description of the range of the prevalence of DD in the general population. This will be done by reviewing the literature on prevalence of DD systematically,

combined with a quality assessment of the included studies. A secondary goal is to perform a meta-analysis on the relation between age and prevalence of DD with data from these studies.

Methods

Literature search

A literature search was performed on 9th of May, 2012 in two bibliographical databases PubMed and Embase. PubMed was searched with the search strategy: ("Dupuytren Contracture"[Mesh] OR dupuytren*[TIAB]) AND ("Prevalence"[Mesh] OR prevalen*[TIAB] OR "Incidence"[Mesh] OR "incidence"[TIAB]). In Embase the following search strategy was imputed: dupuytren*:ab,ti AND ('prevalence'/exp OR prevalen*:ab,ti OR 'incidence'/exp OR 'incidence':ab,ti) NOT [medline]/lim AND [embase]/lim.

The search was updated on 24th of January, 2013 to include new publications, and the updated search was supplemented by automatically weekly derived updates from PubMed until 4th of August. No limits were implemented in our search queries.

Assessment of relevant studies

Two authors (RL and DB) independently assessed the studies in three rounds, based on predefined criteria (Textbox 1). If in the first round inclusion or exclusion criteria could not be assessed from the title and abstract, a full text analysis was performed. Of articles that were included after first evaluation, full text was assessed in two rounds, again by RL and DB separately. After each round, a meeting was held to discuss discrepancies and to reach consensus. The third author (PW) was consulted if no consensus could be reached.

Quality assessment of included studies

We used the scoring instrument of Cho²⁰ to assess the quality of the studies, based on the review article of Shamliyan et al. on quality assessment tools for epidemiologic studies.²¹

The instrument consists of 24 questions about study design, participants, methods to control bias, statistical analyses, reporting of results, and the conclusions drawn from the results.

For each question respectively 2, 1, 0, and 0 points were awarded to the answers "Yes," "Partial," "No," and "Not applicable", in order to obtain an overall quality score for each article.

This was done for each question except for the question on study design; in that case 1 to 5 points were given (1 for case reports, 2 for time series or uncontrolled experiments, 3 for cohort or case-control studies, 4 for nonrandomized control trials, and 5 for randomized control trials).²⁰

Total points awarded for the 24 questions were divided by the total possible points (the sum of the maximum points for each item, excluding "Not applicable" items) to generate a fraction between 0 and 1. A score of 1 represents the highest quality.²⁰

All articles that were included after the second full text round were scored with this instrument by RL and DB independently. The article by Lanting et al. was evaluated by DB and an independent clinical epidemiologist, to avoid a conflict of interest, since both did not participate in that publication.

Data extraction and statistical analysis

In a statistical analysis, we combined studies that provided information on prevalence and sample sizes for different age categories in a total population, or in males and females separately. The aim of this meta-analysis was to determine a population-averaged relationship between age and DD, and to study possible heterogeneity in this relationship between studies. The mid points of the age categories were used in a generalized linear mixed model. The form of the age-prevalence relationship was selected equal to an asymmetric logistic function with a random intercept for study to address possible heterogeneity. This model was applied to the data of males and females simultaneously with a random intercept for males and females that was correlated. A simpler model with only one random intercept was applied to the totals of males and females, since some studies did not provide data separately by gender. From the estimated models and the random effects, a range of age based predicted prevalences were estimated (i.e. 95% prediction intervals). Additionally, in case heterogeneity was present, it was investigated whether the overall quality score or the quality of study design affects the heterogeneity.

In some of the studies, the prevalence was determined in patients with a specific disease, and in a control group. If that was the case, only the data from the control group were used. The calculation of the exact 95% confidence intervals for the overall proportion of DD was calculated using the F-distribution.²²

Results

Results of literature search and assessment of relevant studies

The literature search resulted in 212 articles. After excluding duplicates and critical appraisal of the studies by predefined criteria as mentioned in Textbox 1, 23 studies were included in this review (Figure 1).

Two main reasons led to exclusion: firstly, the prevalence of DD was not determined, and secondly, the study population was not a general population. Consequently, all non-English papers were excluded by this selection.

In Table 1 the details of all included studies are shown. Articles were published between 1972 and 2013. In some studies, only data from the control group were used (noted as CG in Table 1). Several times these control groups were chosen from a population that sustained hand pathology.²³⁻²⁵ In two studies it was explicitly noted that participants in the control group did not suffer from hand pathology.^{26,27}

The total number of participants ranged from 37 to 97.537, in seven studies only males cooperated.²⁸⁻³⁴ Age ranged from 18 to 100 years, with an average above 50 years of age in 12 studies. In six studies age was only reported in age categories, without absolute number of participants in each category, so it was not possible to calculate a mean age (CAT in Table 1).^{25,26,33,35-37}

The lowest prevalence found was 0.6% compared with 31.6% as highest prevalence over all age groups.^{12,38} In the studies of Descatha et al. and Lucas et al., DD was diagnosed in a different fashion compared with the rest of the studies. Descatha et al. did not diagnose palmar thickening as DD, and Lucas et al. excluded the thumb from examination.^{31,32}

The quality score is depicted in the last column of Table 1, this score ranged from 0.23 to 0.80.

Results of quality assessment

Table 2 shows in detail the results of the quality assessment per question, and Table 3 shows the score on the different questions per study. Question 2 is an open question which does not contribute to the final score.

The majority of studies reported the study question only partially. In 13% of the studies the inclusion and exclusion criteria were completely explained, while in 61% these criteria were not depicted at all. In

almost 80% of the papers, the subjects were not randomly selected from the target population, or this was not reported. Only one of the 23 studies reported a sample size justification.³⁹

Regarding the statistical analyses, in almost a quarter of the papers it was not reported which analyses were performed, and in only 52% the performed analyses were fully appropriate to answer the research question. The effect of confounders was most frequently corrected in the statistical analyses, and not beforehand in the study design.

In 70% of the cases the conclusion of the study was fully supported by the findings, however, in one study the results point to a contrary conclusion than reported.²⁵

Explorative analysis

The generalized linear mixed model indicated substantial heterogeneity between studies, meaning that the prevalence varies between studies. It was explored whether the overall quality score, and the sub score on the methods of a study (questions 1, 4, 7-9, 14-17, 19 in Table 3) were related to the heterogeneity. The goal of this analysis was to check whether selecting studies on quality would narrow the prevalence range substantially. The distance of each study to the median profile in Figure 2 was plotted against the variables of interest. No clear pattern was observed for the quality scores or the sub scores; both low quality studies and high quality studies appear on both sides of the median prevalence for all levels. This indicates that the quality of a study did not explain the variance in prevalence, so no studies were excluded for further analyses based on quality score.

Relation between age and prevalence of DD

A combined analysis of 10 studies^{12,15,24-26,35-37,39,42} representing information on prevalences for the population in different age groups showed an overall relationship that is visualized in the upper graph of Figure 2. In the middle and lower graph of Figure 2, this relationship is shown respectively for females (8 studies^{12,15,26,35-37,39,42}) and males (11 studies^{12,15,26,28,29,31,35-37,39,42}). The prevalence is shown as well as the 95% confidence intervals (inner dotted lines), taking into account the heterogeneity between studies. Furthermore, a 95% prediction interval is presented (outer dashed lines), which makes it possible to predict the prevalence at a certain age in the general population. For instance, the overall prevalence of DD is

estimated 12% at 55 years, and 29% at an age of 75 years. The prediction band can be used to estimate the a priori prevalence in a random sample at different ages. Clearly, the prevalence increases with rising age. Furthermore, the graphs show that the prevalence of DD in males is higher than in females. In addition, the age of onset is lower in males compared with the age of onset in females.

Investigating the goodness-of-fit of the estimated models, the R^2 was calculated between the observed numbers of DD, and the predicted numbers of DD from the model. For males the R^2 was estimated at 99.5%, for females the R^2 was equal to 93.0% and for males and females together the R^2 was 97.5%, which demonstrates a good fit of the generalized linear mixed model. This indicates that the models in Figure 2 are able to predict new observations with high certainty. This high goodness of fit may not seem in line with the observed outliers outside the prediction limits in Figure 2. However, several of these outliers were based on small number of subjects (Table 4). For instance, when only one subject is observed in an age category, the prevalence can only be estimated at either 100% or 0% depending on the outcome of DD. The prediction intervals hold true for relative large sample sizes.

Discussion

Dupuytren Disease (DD) is an, often progressive, hand disorder, which can lead to contractures of the affected fingers. Prevalence rates differ widely in the literature, so we felt there was a need for a more thorough analysis. The primary goal of this systematic review was to come to a more accurate distribution of the prevalence of DD in the general population. A secondary goal was to perform a meta-analysis on the relation between age and prevalence of DD.

To our knowledge, this systematic review is the first of its kind, since it focuses on prevalence rates specifically in the general population, and the quality of the studies was critically assessed. Other reviews have been written about prevalence rates of DD, but these reviews concern different kinds of populations, such as manual workers⁴³, rock climbers^{44,45}, and a mixture of healthy participants and patients with a specific disease.¹⁸ Furthermore, we performed a thorough meta-analysis to provide information on the relationship between age and DD.

After initial assessment using predefined inclusion and exclusion criteria, we could include 23 studies investigating the general population, with a number of participants ranging from 37 to 97.537 in the age of 18 to 100 years. Prevalence in these studies varied from 0.6% to 31.6%, which is a smaller range than previously published.¹⁸

During the quality assessment of study design and reporting (see Table 2 and Table 3), we came across a number of noteworthy points. First of all, only few studies mentioned that they applied sampling to select their participants.^{15,23,31,35,39} However, three of these studies did not describe the method of sampling.^{23,31,35} If participants are not randomly selected, this increases the risk of selection bias, and makes it thereby difficult to extrapolate data from the studies. Secondly, only one study reported a sample size justification before the study.³⁹ In an observational study, the accuracy of the estimates, i.e. the prevalence, is dependent on the sample size.⁴⁶ If a sample size calculation is not accomplished on forehand, the results of the study might be less precise than intended. Finally, in only a quarter of the studies the statistical tests were fully stated, and in 52% of the studies the analyses were completely appropriate. To enlarge the reproducibility of the results, it is essential that such information is properly

documented. More importantly, to ensure that correct conclusions will be drawn, it is crucial that appropriate analyses are performed.

In order to narrow the prevalence range, we intended to select studies for further analysis, based on their quality. The final overall quality score differed from 0.23 to 0.80. However, in the explorative analysis, no relation was found between this quality score, and the prevalence that was reported. This is in accordance with the findings in a meta-analysis by Descatha et al., in which the meta-odds ratio for manual work and vibration exposure of all studies was similar to the meta-odds ratio of only high quality studies.⁴³

Several articles have been published about the difficulties using an overall score to assess the quality of a study.⁴⁷⁻⁴⁹ One of the main issues in these articles is that with an overall quality score it is hard to discriminate between poor reporting and poor methodology of the study. Hence, it is advised to evaluate articles based on key components rather than an overall score.^{21,47,50} Therefore, we analyzed the relation between a high score on questions that relate to the methods of a study and the prevalence of DD. Still, no link was found, so we assumed that the current spread in prevalence was not based on a difference in quality of the studies, but on the heterogeneity of the study populations.

We aimed to include studies with participants from the general population. In the majority of studies, participants were actually originating from the general population, such as inhabitants of a specific area. From 11 of the included studies, we used only the data from the control group. In three of these studies²³⁻²⁵, there might have been a chance that participants experienced hand pathology; it is unclear how this affects the prevalence.

As mentioned in the results, in two studies DD was diagnosed differently than in the other studies.^{31,32} Although this did not change our prevalence range substantially, differences in diagnosing DD complicate the comparison of results. Preferably all stages of DD in all rays are taken into account, for example by using the classification of Iselin or Tubiana.^{51,52} Furthermore, there were differences in reporting age; six studies reported age in categories, without giving the actual range.^{25,26,33,35-37} The discrepancies in age reporting also impede comparison of prevalence rates of different studies. Fortunately, we have been able to use data of different age categories in our meta-analysis.

It is well recognized that prevalence of DD increases with rising age, however, until now a thorough analysis on this relationship is lacking. In our meta-analysis, we investigated this relationship by using all

studies that provided information on prevalence of DD in different age categories. We have been able to present the relationship between age and DD, including 95% confidence intervals and 95% prediction intervals. The figures can be used to determine a common estimate and prediction interval for the prevalence of DD at different ages, both for the total population as well as for males and females separately. Nowadays, still little is known about the prevalence of DD in younger people of the general population, because one of the inclusion criteria in most studies was that participants appeared over fifty years of age. However, the relationship between age and prevalence presented in this paper already provides a first indication for prevalence at younger age.

Conclusion

The prevalence of DD in the general population ranges from 0.6% to 31.6%. With the results of our meta-analysis, we have been able to present the relationship between prevalence of DD and age, including confidence intervals and prediction intervals. With the presented graphs it is possible to determine the prevalence at a certain age for the total general population, and for men and women separately.

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Textbox 1. Criteria for inclusion and exclusion

Round 1. Title and abstract

Inclusion criteria:

- DD as research theme
- General population as sample

Exclusion criteria:

- Case report
- Case series
- Review article
- Subjects aged <18 years

Round 2. First full text assessment

Inclusion criteria:

- Prevalence of DD as research theme

Exclusion criteria:

- Age is not reported
- Physical examination to diagnose DD was not performed or not reported
- Full text is not available

Round 3. Second full text assessment

Inclusion criteria:

- Prevalence is calculated
- Data is provided to calculate prevalence

Exclusion criteria:

- Unclear how DD is diagnosed
- Outcome is 'Dupuytren Contracture', not further specified
- Incidence was reported instead of prevalence

DD: Dupuytren Disease

Figure 1. Flow-chart of study selection procedure.

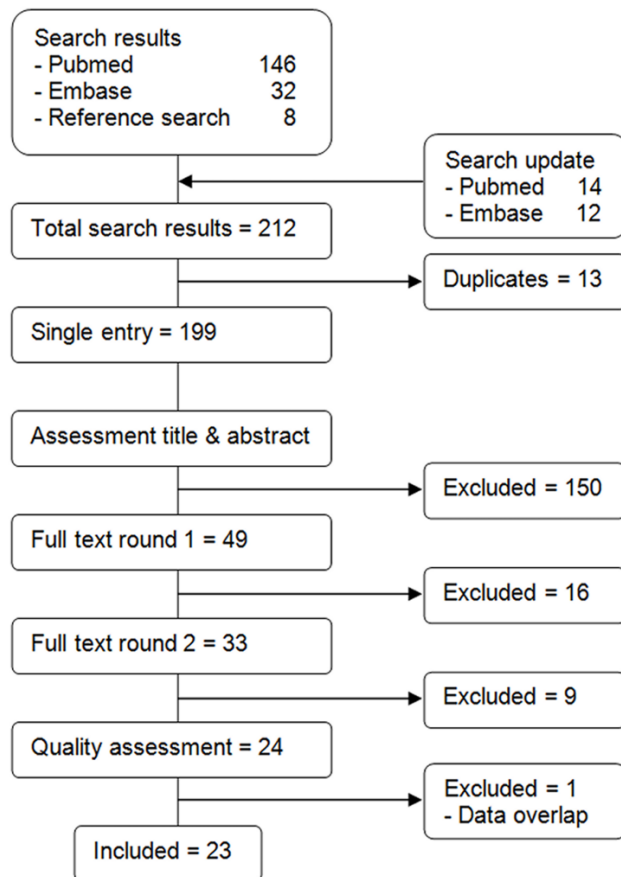


Table 1. Details of included studies.

Authors	Year	Population	N	Gender	Age			Prevalence (95%CI)	Quality score
					Mean	SD	Range		
Arafa ³⁵	1984	Patients of fracture clinic (CG)	555	F and M	CAT			16.0 [13.1 ; 19.4]	0.46
Ardic ²³	2003	Non-diabetic patients of department of physical medicine and rehabilitation (division rheumatology) (CG)	37	F and M	55.7	11.5	30-79	2.7 [1.0 ; 14.2]	0.44
Attali ⁴⁰	1987	Patients of gastroenterology unit without alcoholism or chronic liver disease (CG)	174	F and M	58.9	22.7		12.5 [8.1 ; 18.5]	0.49
Aydeniz ⁴¹	2008	Non-diabetic patients of public health clinic (CG)	101	F and M	60.1	7.6		4.0 [1.1 ; 9.8]	0.51
Bennett ²⁸	1982	Workers PVC manufacturing plant not involved with bagging or packing (CG)	84	M	40.1			1.19 [0.0 ; 6.5]	0.46
Burke ²⁹	2007	Miners seeking compensation for Hand-Arm Vibration Syndrome	97537	M	53.5			8.13 [8.0 ; 8.30]	0.62
Carson ³⁰	1993	Ex-military service pensioners in the Royal Hospital Chelsea	400	M	75.9		65-99	13.8 [10.5 ; 17.5]	0.38
Degreef ¹²	2010	Visitors of markets in Flanders, Belgium	500	F and M	70.4		50-100	31.6 [27.5 ; 35.9]	0.46
Descatha ³¹	2012	Employees in private sector in Pays de la Loire, France	2161	M	38.5		20-59	1.25 [0.8 ; 1.8]	0.66
Eadington ¹³	1989	Normotensive, non-diabetic subjects, selected from inpatients, outpatients and hospital staff members (CG)	150	F and M	51.2	17.4		18.0 [12.2 ; 25.1]	0.64
Finsen ³⁶	2002	Residents of rural municipalities in Norway	456	F and M	CAT		50-80+	7.5 [5.05 ; 9.87]	0.51
Gudmundsson ¹⁵	2000	Residents of Reykjavik and adjacent communes, Iceland	2165	F and M	57.5		45-94	13.3 [11.9 ; 14. 8]	0.56

Lanting ³⁹	2013	Residents of Groningen, The Netherlands	763	F and M	62 (median)	56-69 (IQR)	22.1 [19.3 ; 25.3]	0.80
Lennox ²⁶	1993	Patients on geriatric ward, not admitted for hand pathology	200	F and M	CAT		30.0 [23.7 ; 36.9]	0.37
Lucas ³²	2008	Civil servants of Pays de la Loire and Brittany, France	2406	M	45.3	7.6	8.8 [7.7 ; 10.0]	0.64
Mikkelsen ⁴²	1972	Residents of Haugesund, Norway	15950	F and M	45.0	16-99	5.6 [5.3 ; 6.0]	0.46
Noble ²⁵	1992	Patients of fracture clinic (CG)	100	F and M	CAT	.	8.0 [3.5 ; 15.2]	0.36
Noble ²⁴	1984	Patients of fracture clinic (CG)	150	F and M	57.4		18.0 [12.2 ; 25.1]	0.28
Pal ²⁷	1987	Non-diabetic subjects without musculoskeletal complaints (CG)	75	F and M	44.0 (median)	18-76	9.0 [3.8 ; 18.3]	0.49
Rafter ³³	1980	Inpatients in acute medical and surgical wards	403	M	CAT	.	17.1 [13.6 ; 21.2]	0.23
Ravid ³⁸	1977	Non-diabetic patients of different departments of medicine (CG)	1396	F and M	52.0	19-86	0.6 [0.3 ; 1.2]	0.49
Thomas ³⁴	1992	Patients admitted to general surgical ward (CG)	150	M	64.1	50-85	10.7 [6.2 ; 16.7]	0.46
Zerajic ³⁷	2004	Visitors of public places in both urban and rural areas of Bosnia Herzegovina	1207	F and M	CAT	.	25.4 [23.0 ; 28.0]	0.59

CG: control group, N: number of participants, SD: standard deviation, CI: confidence interval, IQR: inter quartile range,
CAT: age reported only in categories.

Table 2. Quality assessment of included studies per question.

Answer:		Yes		Partial		No		NA	
Question		n	%	n	%	n	%	n	%
1	Study design †								
2	What was the study question? ‡								
3	Was the study question sufficiently described?	5	22%	15	65%	3	13%	0	0%
4	Was the study design appropriate to answer the study question?	21	91%	2	9%	0	0%	0	0%
5	Were both inclusion and exclusion criteria specified?	3	13%	6	26%	14	61%	0	0%
6	For case studies only: Were patient characteristics adequately reported?*	0	0%	0	0%	0	0%	23	100%
7	Were subjects appropriate to the study question?	19	83%	4	17%	0	0%	0	0%
8	Were control subjects appropriate?	12	52%	6	26%	5	22%	0	0%
9	Were subjects randomly selected from the target population?	5	22%	0	0%	18	78%	0	0%
10	If subjects were randomly selected, was the method of random selection sufficiently well described?	1	4%	1	4%	3	13%	18	78%
11	If subjects were randomly allocated to treatment groups, was method of random allocation sufficiently described?**	0	0%	0	0%	0	0%	23	100%
12	If blinding of investigators was possible, was it reported?***	0	0%	0	0%	0	0%	23	100%
13	If blinding of subjects to intervention was possible, was it reported?***	0	0%	0	0%	0	0%	23	100%
14	Was measurement bias accounted for by other methods than blinding?	6	26%	11	48%	6	26%	0	0%
15	Were known confounders accounted for by study design?	5	22%	3	13%	13	57%	2	9%
16	Were known confounders accounted for by analysis?	9	39%	5	22%	7	30%	2	9%
17	Was there a sample size justification before the study?	1	4%	0	0%	22	96%	0	0%
18	Were post hoc power calculations or confidence intervals reported for statistical non significant results?	4	17%	4	17%	15	65%	0	0%

19	Were statistical analyses appropriate?	12	52%	5	22%	6	26%	0	0%
20	Were the statistical tests stated?	6	26%	12	52%	5	22%	0	0%
21	Were exact values or confidence intervals reported for each test?	5	22%	13	57%	5	22%	0	0%
22	Were attrition of subjects and reason for attrition recorded?	4	17%	3	13%	16	70%	0	0%
23	For those subjects who completed the study; were results completely reported?	15	65%	7	30%	1	4%	0	0%
24	Do the findings support the conclusions?	16	70%	6	26%	1	4%	0	0%

n: number of studies, %: percentage, NA: not applicable, † See Table 3, ‡ Open question which does not contribute to final score, * Case studies were not included, so question 6 was not applicable for each of the included articles, ** Questions were not applicable, because this concerns intervention studies.

Table 3. Quality assessment of included studies per study.

Author	Questions†																							
	1	2‡	3	4	5	6*	7	8	9	10	11**	12**	13**	14	15	16	17	18	19	20	21	22	23	24
Arafa ³⁵	2		0	1	0	NA	2	1	2	0	NA	NA	NA	2	2	1	0	0	0	1	1	0	2	2
Ardic ²³	2		1	2	0	NA	2	0	2	0	NA	NA	NA	1	0	2	0	0	1	1	0	0	2	2
Attali ⁴⁰	2		1	2	0	NA	2	2	0	NA	NA	NA	NA	0	0	2	0	0	2	1	1	0	2	2
Aydeniz ⁴¹	2		1	2	1	NA	2	2	0	NA	NA	NA	NA	2	2	0	0	0	1	1	1	0	2	1
Bennett ²⁸	2		1	2	0	NA	2	2	0	NA	NA	NA	NA	1	0	2	0	0	1	1	0	0	2	2
Burke ²⁹	2		2	2	0	NA	2	2	0	NA	NA	NA	NA	1	0	2	0	2	2	2	2	0	1	2
Carson ³⁰	2		0	2	0	NA	2	2	0	NA	NA	NA	NA	1	0	1	0	0	0	0	1	0	2	2
Degreef ¹²	2		1	2	2	NA	2	2	0	NA	NA	NA	NA	2	0	0	0	0	0	0	1	0	2	2
Descatha ³¹	2		1	2	2	NA	2	2	2	0	NA	NA	NA	1	0	2	0	2	2	1	1	1	2	2
Eadington ¹³	2		2	2	2	NA	2	1	0	NA	NA	NA	NA	1	1	2	0	1	2	2	1	1	2	1
Finsen ³⁶	2		1	2	1	NA	2	0	0	NA	NA	NA	NA	0	0	1	0	1	2	2	2	2	1	1
Gudmundsson ¹⁵	3		1	2	0	NA	2	2	2	1	NA	NA	NA	1	0	2	0	1	2	1	1	0	1	1
Lanting ³⁹	2		2	2	0	NA	2	2	2	2	NA	NA	NA	1	2	2	2	2	2	2	2	0	2	2
Lennox ²⁶	2		1	2	0	NA	1	0	0	NA	NA	NA	NA	1	NA	NA	0	0	1	1	1	0	1	2
Lucas ³²	2		1	2	1	NA	1	2	0	NA	NA	NA	NA	1	0	2	0	2	2	2	2	1	2	2
Mikkelsen ⁴²	2		1	2	1	NA	2	0	0	NA	NA	NA	NA	2	NA	NA	0	0	0	0	0	2	2	2
Noble ²⁴	2		0	2	0	NA	2	1	0	NA	NA	NA	NA	0	2	0	0	0	0	0	1	0	0	1
Noble ²⁵	2		1	2	0	NA	1	1	0	NA	NA	NA	NA	0	1	0	0	0	2	1	1	0	2	0
Pal ²⁷	2		2	2	1	NA	2	2	0	NA	NA	NA	NA	2	0	0	0	0	1	1	1	2	1	0
Rafter ³³	2		1	1	0	NA	1	2	0	NA	NA	NA	NA	0	0	0	0	0	0	0	0	0	1	1
Ravid ³⁸	2		2	2	0	NA	2	1	0	NA	NA	NA	NA	0	2	1	0	0	2	1	0	0	2	2
Thomas ³⁴	2		1	2	0	NA	2	1	0	NA	NA	NA	NA	1	0	1	0	0	2	1	2	0	1	2
Zerajic ³⁷	2		1	2	1	NA	2	0	0	NA	NA	NA	NA	2	1	0	0	1	2	2	1	2	2	2

† Questions: **1:** Study design, **2:** Research question, **3:** Study question sufficiently described, **4:** Study design appropriate to answer study question, **5:** Inclusion and exclusion criteria specified, **6:** Case studies: patient characteristics adequately reported, **7:** Subjects appropriate to study question, **8:** Control subjects appropriate, **9:** Random selection of subjects, **10:** Method of random selection sufficiently well described, **11:** Random allocation to treatment group sufficiently described, **12:** Blinding of investigators to intervention reported, **13:** Blinding of subjects to intervention reported, **14:** Measurement bias accounted for by methods other than blinding, **15:** Known confounders accounted for by study design, **16:** Known confounders accounted for by analysis, **17:** Sample size justification, **18:** Post hoc power calculations or confidence intervals reported for statistically non significant results, **19:** Appropriate statistical analyses, **20:** Statement of statistical tests, **21:** Exact values of confidence intervals reported for each test, **22:** Reporting of attrition of subject and reason for attrition, **23:** Results completely reported for subjects who completed the study, **24:** Findings support the conclusion.

Question 1 was scored 3 (cohort design) or 2 (cross-sectional design), other questions were scored 2 (yes), 1 (partial), 0 (no), NA (not applicable).

The score was calculated by dividing the total points by the maximum possible points. A higher score represents a higher quality.

‡ Open question which does not contribute to the final score.

* Case studies were not included, so question 6 was not applicable for each of the included articles.

** Questions were not applicable, because this concerns intervention studies.

Figure 2. Relationship between age and DD. Upper graph: totals, middle graph: females, lower graph: males. Bold line: estimated prevalence, dotted line: 95% confidence interval, dashed line: 95% prediction interval, dots: individual prevalence estimates used in the analysis.

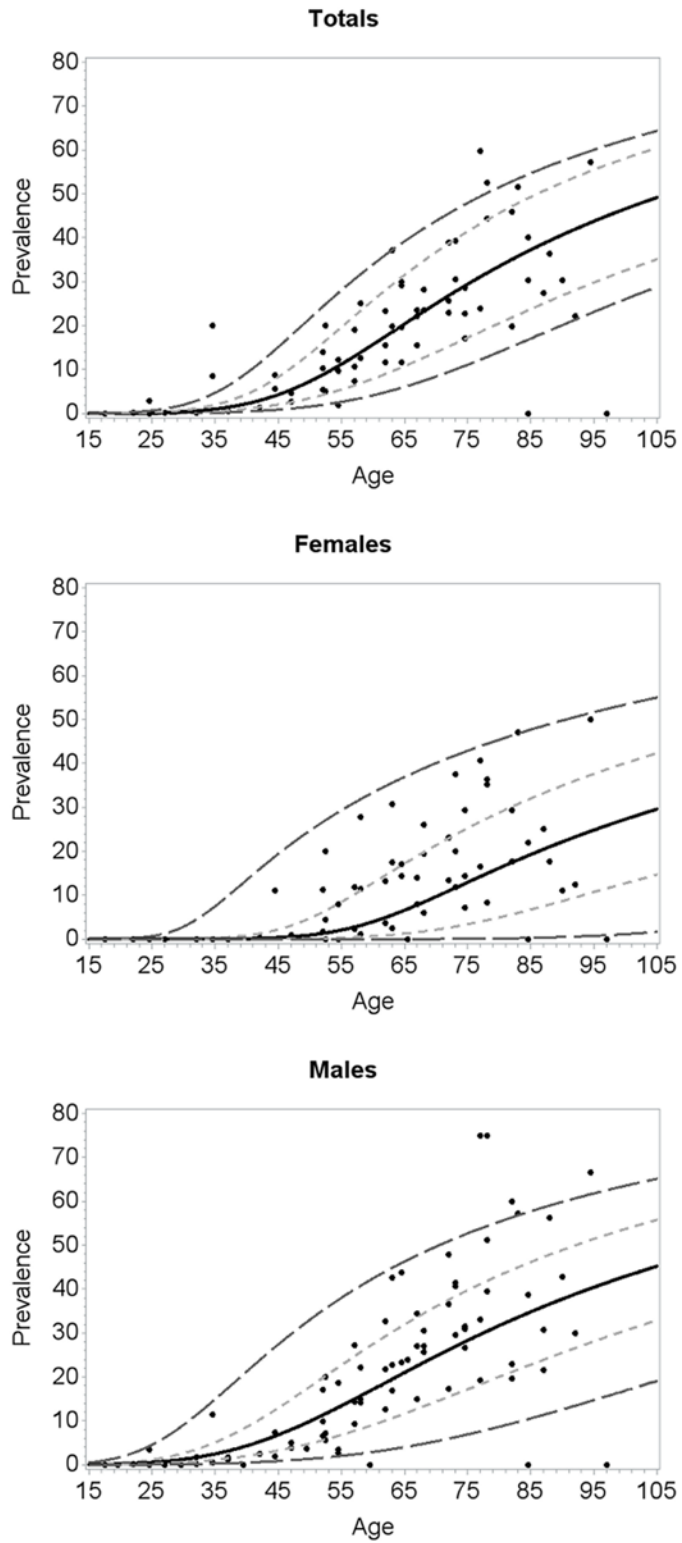


Table 4. Studies outside prediction intervals

Population	Age cat.	Author	n DD	n total	% DD	95% PI
Total	<30	Arafa	1	34	2.94	0.02 – 0.61
	30-34	Mikkelsen	1	1043	0.10	0.12 – 2.89
	30-39	Arafa	4	47	8.51	0.18 – 4.38
	30-39	Noble (1984)	1	5	20	0.18 – 4.38
	50-59	Finsen	2	103	1.94	2.53 – 27.46
	61-65	Degreef	32	86	37.21	5.25 – 37.20
	75-79	Zerajic	43	72	59.72	12.26 – 49.43
	76-80	Lanting	30	57	52.63	12.84 – 50.15
	>80	Finsen	0	24	0	16.76 – 54.41
	95-99	Mikkelsen	0	3	0	24.32 – 60.98
Males	<30	Descatha	0	491	0	0.06 – 4.22
	55-64	Bennet	0	9	0	2.84 – 42.03
	75-79	Zerajic	30	40	75	7.60 – 53.80
	76-80	Lanting	18	24	75	7.95 – 54.34
	>80	Finsen	0	7	0	10.38 – 57.52
	80+	Zerajic	24	40	60	9.41 – 56.35
	81-85	Lanting	8	14	57.14	9.80 – 56.83
	>90	Lennox	4	6	66.67	14.52 – 61.62
	90-94	Mikkelsen	1	1	100†	13.45 – 60.68
	95-99	Burke	0	1	0	15.60 – 62.53
	95-99	Mikkelsen	0	1	0	15.60 – 62.53
Females	81-85	Lanting	8	17	47.06	0.25 – 46.83

Age cat: age category, n DD: participants with DD, n total: total participants, % DD: percentage of participants with DD, 95% PI: 95% prediction interval

† Outlier not visible in Figure 2 (Y-axis ranges from 0-80%)